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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/988,013	11/16/2001	Shui-on Leung	18733/1082	7681

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 11/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/988,013	LEUNG ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 30 June 2005 has been entered.

2. Claims 1-27 are canceled.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Rejections.

5. Claims 28-32 are pending and under examination.

Response to Arguments

6. All objections and rejections presented in the previous Office Action mailed 3/30/2005 are withdrawn in view of the amendments to the specification and the cancellation of the claims.

New Grounds of Objections/Rejections

Specification

7. The abstract of the disclosure is objected to because it exceeds 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited.

Correction is required. See MPEP § 608.01(b).

8. a. The specification at page 9 is objected to as containing a USSN 08/162,912, which is now US Patent 5,443,953. Applicant is required to update USSN 08/162,912 with the corresponding US patent number, US Patent 5,443,953.

b. The specification at page 10, line 17 is missing a space between the terms "is" and "incorporated". Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 28-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 28-32 are ambiguous in the recitation of "determining residue identities...using computer modeling" in claim 28. It is unclear what is contemplated because computer modeling provides the skilled artisan with a three-dimensional structure of the antibody wherein the spatial arrangement of the individual amino acids

may be determined (see Fig 2), however, computer modeling would not provide a direct comparison of the amino acid sequences/primary structure such that one skilled in the art could readily determine residue identities. Does "computer modeling" mean that the murine LL2 variable domain sequences are compared to the corresponding human variable domain sequences in a database of sequences?

b. Claims 28-32 are indefinite in the recitation of "A method of designing an amino acid sequence of a variable domain of a humanized monoclonal antibody..."obtaining amino acid sequences of the variable domains of the light and heavy chain regions of the resultant humanized monoclonal antibody" in claim 28. Are both the humanized heavy and light chain variable domains designed in the claimed method or is the method drawn to the design of only one humanized variable domain of the humanized antibody as recited in the preamble?

11. Claims 28-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The response filed 6/30/2005 has introduced NEW MATTER into the claims. Newly added claims 28-32 recite that the method of designing a variable domain of a humanized antibody wherein residue identities between the amino acid sequences of a variable domain of a monoclonal antibody to be humanized and the corresponding

variable domains of two or more human monoclonal antibodies are determined using computer modeling and the framework regions are selected from two or more of the human monoclonal antibodies and have approximately 75 to 92.3% sequence identity with the corresponding framework regions in the monoclonal antibody to be humanized (see parts (a) and (b) of claim 28). The response filed 6/30/2005 pointed to paragraphs [0043], [0044]-[0046], [0048], [0053] and [0067] of the as filed disclosure for support for newly added claims 28-32. Upon review of the instant disclosure as filed there is inadequate written support for the presently claimed methods of designing and producing a humanized monoclonal antibody. The disclosure as filed only contemplates humanization of the LL2 antibody in the context of REI light chain framework regions and EU and NEWM heavy chain framework regions (see Example 1, in particular). There is insufficient written description pertaining to the claimed methods of designing and producing the genus of humanized antibodies as encompassed by the claims. Additionally, there is inadequate written support for the human framework regions that have approximately 75 to 92.3% sequence identity with the corresponding framework regions in the monoclonal antibody to be humanized. The residue identity range of 75 to 92.3% is disclosed at paragraph [0043] only when comparing the framework sequences of the murine LL2 light chain and human REI light chain framework regions in the context of modeling the 3-D structure. Further, Figure 1 discloses that the asterisks indicate murine framework region sequences that are different from that of the human framework regions at corresponding positions, meaning that murine LL2 FR1 is only 69%, FR3 is 72 % and FR4 is 72% identical to the corresponding framework

regions of the REI sequence (see Figure 1 and legend). Additionally, there is no disclosure of the human heavy chain framework sequences having approximately 75 to 92.3% sequence identity with the corresponding framework regions in the monoclonal antibody to be humanized. Figure 1 also discloses that murine LL2 framework regions 1-4 have 73%, 71%, 62.5% and 91% sequence identity, respectively, with the corresponding framework regions of EU (FR1-3) and NEWM for FR4 (again the asterisks indicate murine LL2 framework sequences that are different from that of the corresponding human framework sequence). Thus, there is insufficient written support for the range of "approximately 75 to 92.3%" as presently recited. In addition, there is insufficient written support for determining residue identities between the variable domains of the non-human monoclonal antibody and the human monoclonal antibodies from which the framework regions are selected for humanization using computer modeling. The disclosure of computer modeling is with respect to determining the vicinal relationships of the LL2 CDRs to their framework regions to identify murine framework residues having potential CDR contacts, which might affect the antigen binding function of the humanized antibody and should be retained in the humanized framework sequences (see paragraph [0043], Fig. 2 and legend, and Example 1). There is inadequate written support for using computer modeling for determining residue identities between the variable domains of the non-human monoclonal antibody and the human monoclonal antibodies from which the framework regions are selected for humanization.

Newly added claims 28-32 now recite limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in newly added claims 28-32, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to provide sufficient written support for the limitations recited in newly added claims 28-32 in the specification or claims, as filed, or remove these limitations from the claims in response to this Office Action.

Applicant is reminded that obviousness is not the standard for the addition new limitations to the disclosure as filed. It is noted that entitlement to a filing date does not extend to subject matter, which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

12. Claims 28-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Queen et al (WO 90/07861, 7/26/1990) in view of Adair et al (US Patent 5,859,205 9/17/1991).

The claims are interpreted as being drawn to a method of designing an the amino acid sequences of the variable domains of a humanized antibody comprising determining residue identities between that amino acid sequences of the variable domains of a non-human monoclonal antibody to be humanized and the corresponding variable domains of two or more human monoclonal antibodies using computer

modeling (interpreted as a computer database or data bank of human sequences, due to the indefinite nature of the claims); selecting framework regions from two or more of said corresponding variable domains wherein each framework region has a sequence identity of approximately 75 to 92.3% to the corresponding framework region in the non-human monoclonal antibody to be humanized; incorporating the selected framework regions with the CDRs of the non-human monoclonal antibody to be humanized; retaining selected amino acids from the framework regions of the non-human monoclonal antibody if one or more of said selected amino acids are predicted to have contacts with said CDRs affecting the affinity and specificity of the resultant humanized antibody or within a 4.5 Angstrom radius of the CDRs; and obtaining amino acid sequences of the variable domains of the light and heavy chain regions of the resultant humanized monoclonal antibody and wherein at least three of said selected framework regions are from different human monoclonal antibodies and wherein two or more of the selected human heavy chain framework regions are from the heavy chain region of different human monoclonal antibodies. Further, claim 32 is drawn to a process of producing a humanized monoclonal antibody designed as above comprising the additional steps of preparing a DNA sequence encoding the variable domains of the resultant humanized monoclonal antibody based upon the designed amino acid sequence; operably incorporating the DNA sequences into at least one vector comprising the constant domains of the light and heavy chain regions; introducing the vector into a cell; and culturing the cell under conditions to produce the humanized monoclonal antibody.

Queen et al teach a method of designing the amino acid sequences of the variable domains of a humanized antibody comprising determining the most homologous human variable domains in a data bank compared to the non-human variable domains (i.e., interpreted as determining residue identities using computer modeling); selecting the most homologous human framework regions (i.e., acceptor immunoglobulin), which may be a consensus framework from many human antibodies (i.e., framework regions from two or more human antibodies); incorporating the selected framework regions with the CDRs of the non-human monoclonal antibody to be humanized (i.e., donor immunoglobulin) and retaining selected framework amino acids from the non-human monoclonal antibody that are predicted to be able to interact with the CDRs of humanized antibody or are within about 3 Angstroms of the CDRs of the humanized antibody (see pages 11-15). Queen et al also teach the production of the humanized antibody comprising preparing recombinant DNA segments encoding the designed humanized variable domains, operably incorporating the DNA sequences into at least one vector comprising the constant domains of the light and heavy chain regions, introducing the vector(s) into host cells and culturing the host cells under conditions to produce the humanized antibody (see pages 16-20). Queen et al do not specifically teach selecting human framework regions from two or more variable domains wherein each selected human framework region has a sequence identity of approximately 75 to 92.3% to the corresponding framework regions of the donor antibody (i.e., non-human monoclonal antibody to be humanized). This deficiency is made up for in the teachings of Adair et al.

Adair et al teach antibody humanization using framework regions selected from two or more different human variable domains, including the REI frameworks for the light chain and the EU frameworks for the heavy chain framework regions 1-3 and a consensus human sequence for FR4 of the heavy chain in place of EU FR4 (see Example 3, column 28 in particular).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have selected human framework regions from two or more human variable domains wherein each framework region has a sequence identity of approximately 75 to 92.3% to the corresponding framework regions of the donor antibody in the method of Queen et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have selected human framework regions from two or more human variable domains wherein each framework region has a sequence identity of approximately 75 to 92.3% to the corresponding framework regions of the donor antibody in the method of Queen et al because Queen et al teach using a consensus framework from many human antibodies and selecting the most homologous human framework regions as the acceptor immunoglobulin has the advantages of fewer amino acids will be changed in going from the donor (i.e., non-human) immunoglobulin to the humanized immunoglobulin, and hence there is a smaller chance of changing an amino acid near the CDRs that distorts their conformation and the overall shape of the humanized antibody may more closely resemble the shape of the donor antibody, also reducing the chance of distorting the

CDRs (see pages 12-14) and Adair et al teach the use of different framework regions for antibody humanization, including using human REI framework regions for the light chain humanization and human EU framework regions for framework regions 1-3 and a consensus human sequence for framework region 4 of the humanized heavy chain since framework region 4 of EU is unlike that of any other human or mouse antibody. Therefore, one of ordinary skill in the art would have been motivated and had a reasonable expectation of success at the time the invention was made to have selected the most homologous human framework regions from two or more of the corresponding human variable domains, which have approximately 75 to 92.3% sequence identity with the corresponding non-human framework sequences in order to minimize the amino acid differences in the selected human framework regions for antibody humanization in order to avoid amino acid changes that result in a loss of antibody affinity and minimize the number of human framework residues that have to be back-mutated to the corresponding non-human framework residues to keep all antigen contacts that provide affinity in the original non-human antibody. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have selected human framework regions from two or more human variable domains wherein each framework region has a sequence identity of approximately 75 to 92.3% to the corresponding framework regions of the non-human antibody to be humanized in view of Queen et al and Adair et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature, matching or filed papers or relating to the status of this application or proceeding should be directed to Tony Parks for Art Unit 1643 whose telephone number is 571-272-0543.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER